



Downstaging unresectable hepatocellular carcinoma by radioembolization using 90-yttrium resin microspheres: a single center experience

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Background: Only one third of patients with hepatocellular carcinoma can benefit from curative treatments at the time of first diagnosis. Tumor downstaging by radioembolization may enable initially unresectable hepatocellular carcinoma (HCC) to be treated with surgery lengthening survival.

Methods: From June 2011 through June 2014, all patients with a first diagnosis of unresectable HCC with intrahepatic portal vein thrombosis were treated in our center with radioembolization using 90-yttrium resin microspheres. A 3-year enrollment period and a 5-year follow-up were planned to adequately investigate survivals.

Results: Twenty-four patients were enrolled, five were downstaged to surgery, eight did not reach downstaging but achieved partial response or stable disease, and eleven showed HCC progression despite radioembolization. High tumor absorbed radiation doses (454 vs. 248 and 138 Gy, $P=0.005$) and low serum AFP levels (53 vs. 1,447 and 4,603 ng/mL, $P=0.05$) were the variables significantly associated with successful downstaging. Mean and median survivals were 54, 30 and 11 months and 70, 24 and 11 months in the three groups respectively. No severe side effects were registered.

Conclusions: In our center, about 20% of patients with locally advanced unresectable hepatocellular carcinoma were successfully downstaged to surgery after radioembolization. This strategy increases survival and is associated with an excellent safety profile.

Keywords: Radioembolization; hepatocellular carcinoma; downstaging

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Despite a slight but continuous decrease in incidence, HCC remains among the top five causes of cancer-related death in Italy (1). Despite surveillance recommendations, a high number of HCC are diagnosed at an advanced stage and only one third of them may benefit of curative treatments (2,3). Tumor

downstaging through the use of loco-regional treatments may allow unresectable tumor to be resectable, providing the best chance of cure to these patients (4). The 5-year survival rate following tumor downstaging and salvage surgery is similar to the survival rate for patients with initially resectable HCC (5). Downstaging is the result of a treatment that makes possible a surgical procedure that would otherwise be impossible or too risky; mainly for

anatomical reasons or for insufficient remnant liver or for presence of macrovascular portal or hepatic vein invasion.

Transarterial radioembolization (TARE) has some peculiarities that make it attractive for downstaging strategy. It has been reported to induce an efficient and rapid decrease in tumor size with few occurrences of post-embolization syndrome and a low number of treatments, to prolong time to progression of the tumor and to induce long survivals (6-9). TARE can induce a significant hypertrophy of the contralateral hepatic lobe (10-12) and it is to be preferred in presence of portal vein thrombosis (PVT) for its lower risk of liver ischemia (13-15). Finally, the delay from downstaging treatment to surgery (test of time) allows physicians to select those patients with a favourable biology for surgical intervention, decreasing the chance of early recurrence in the remnant liver. The goal of this study was to examine survival of patients with unresectable HCC and PVT consecutively treated with TARE with the aim to downstaging them to a curative surgical treatment. A 3-year enrollment period and a 5-year follow-up were planned in order to adequately investigate survival.

Methods

Patients

All consecutive patients who offered from June 2011 through June 2014 to our center with a first diagnosis of unresectable HCC with PVT were treated. Inclusion criteria were a well-preserved liver function (Child-Pugh A), platelet count $>100,000$ c/ μ L, international normalized ratio (INR) <1.5 . Exclusion criteria was the extension of the tumor thrombus to the main trunk of the portal vein. Unresectability and downstaging were evaluated by the same surgeons at enrollment. Eligibility for surgery were re-evaluated by the same surgeons at 6 and 12 months after TARE. A second TARE was performed if indicated. The treatment protocol was approved by our Institution Ethical Committee and all patients provided informed consent.

Trans-arterial radio-embolization

A planning simulation was performed to determine the optimal tumoricide dose and avoid excessive irradiation of the surrounding liver and determine the extent of extra-hepatic shunting. Patients were subjected to an angiographic evaluation to detect collateral vessels feeding extra-hepatic organs and a subsequent infusion of technetium-99-labeled

macroaggregated albumin (LyoMAA, Mallinckrodt Med, NL, USA) which mimics the vascular distribution pattern of ^{90}Y microspheres. A total body planar image and a proton emission computed tomography (SPECT/TC) (Siemens SymbiaIntevo, IterativeFlash3D attenuation and scatter corrected) were acquired. Radioembolization was performed according to the standardized procedure (16) with resin microspheres (Sirtex Medical Europe GmbH).

Dosimetry

Activities were calculated according to the multi-compartmental (MIRD) model and the voxel-based method with the aim of delivering the highest dose to the tumor, while not exceeding 40 Gy to the surrounding liver parenchyma and 30 Gy to the lung (17,18). The MIRD model used pre-treatment $^{99\text{mTc}}$ -MAA SPECT-CT images: two volume of interest (VOIs) were drawn on images to estimate $^{99\text{mTc}}$ -MAA uptakes and volumes of the tumor and remnant liver parenchyma. The voxel dosimetry used the SPECT-3D corrected counts matrix. A MATLAB (Mathworks) code was developed within our department. Convolution calculations were adopted: for each targeted voxel, the mean absorbed dose from surrounding source voxels along three major axis was calculated. Twenty-four hours after ^{90}Y injection, a bremsstrahlung SPECT-TC was performed to verify the correct microspheres distribution comparing it with the simulation phase and the absorbed dose (Gy) was calculated.

Follow-up and safety

Patients were assessed monthly for the first 6 months following TARE and then every 6 months. Hepatic function, serum α -fetoprotein (AFP) were assessed and medical examinations were performed. During the second month after TARE, a quadriphasic CT was performed to assess the response. Response evaluation criteria in solid tumors (mRECIST) and the EASL criteria on vascular enhancement were applied to assess treatment response (19,20). Thereafter, CT scans, hepatic functions assessment and medical examination were performed at 6 month and then every six months. All adverse events (AEs) were classified for severity by using the National Cancer Institute Common Toxicity Criteria (CTCAE3.0) (21). All grade 3 or greater adverse effects occurring within 30 days were considered to be treatment-related.

Table 1 Baseline characteristics of patients with HCC assigned to post-TARE group based on tumor response

Group	Downstaged	Partial response/stable disease	Progressive disease	P value
Patients' number	5	8	11	
Age (mean, range) (years)	74 [64–75]	67 [51–78]	71 [53–86]	0.701
Male sex (number, %)	5/5 (100.0)	7/1 (87.5)	9/2 (82.0)	0.595
Etiology (viral/metabolic) (%)	80/20	60/40	56/44	0.226
INR	1.0±0.07	1.0±0.1	1.0±0.16	0.455
Bilirubin (mg/dL)	1.0±0.69	0.8±0.41	1.0±0.16	0.455
Albumin (g/L)	3.6±0.3	3.7±0.4	4.0±0.4	0.642
Creatinine (mg/dL)	0.9±0.08	0.7±0.17	0.8±0.1	0.462
MELD	7±1.5	7±1.1	7±1.2	0.967
Tumor				
Max diameter (mm)	70±15	65±32	64±30	0.93
Number of nodules	2 [1–3]	2 [1–5]	4 [1–6]	0.379
PVT (grade 1–2/3–4)	4/1	4/4	3/8	
Alpha-fetoprotein (ng/mL)	53±86	1,447±2,337	4,603±8,619	0.05

HCC, hepatocellular carcinoma; TARE, transarterial radioembolization; INR, international normalized ratio; MELD, model for end-stage liver disease; PVT, portal vein thrombosis.

Statistical analysis

Patients' characteristics were reported using frequency and descriptive analysis when appropriate. All statistical analysis were performed using IBM SPSS Statistics for Windows, Version 2.0 Italian. The differences between continuous variables were assessed with the Kruskal-Wallis test. Follow-up was calculated from the date of treatment to the date of death or the last visit. The Kaplan-Meier method was used to analyse survival. $P < 0.05$ was considered as statistically significant. Data were censored at August 2018.

Results

Initially, 28 patients were enrolled, however, after the simulation session 4 patients were excluded because of the presence of excessive pulmonary shunt or intrahepatic arterio-venous fistulas. Thus, 24 patients were treated using TARE with resin microspheres. All the patients had cirrhosis. At the 6-month follow-up, 2 patients had HCC downstaged and underwent surgery. Sixteen patients had radiological response with 7 requiring a second TARE procedure and the remaining 6 patients showed progression of HCC. At the 12-month follow-up, 3 additional patients had HCC

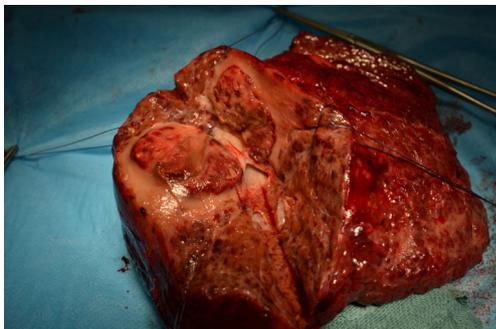
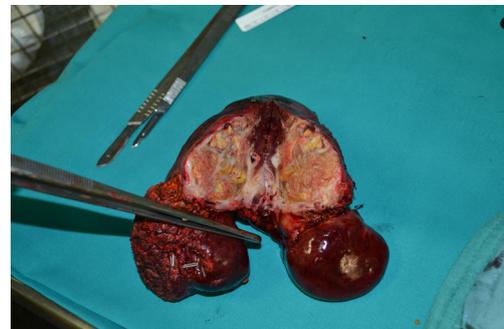
downstaged and underwent surgery, 8 maintained partial response or stable disease and 5 additional patients had HCC progression. A total of 5 patients (21%) had HCC that were successfully downstaged (group 1), 8 patients (33%) (group 2) demonstrated radiological responses (partial response or stable disease) but did not become eligible for surgery due to worsening of liver function (6 patients) or due to reduction of platelet count (2 patients). Eleven patients (46%) had progressive disease despite TARE (group 3).

Pre-treatment clinical parameters, liver function tests and tumor size were not significantly different among the three groups (Table 1). Serum AFP levels were significantly higher in patients with progressive disease ($P = 0.05$). In contrast, high tumor absorbed doses (Gy) were significantly associated with more favourable outcomes to TARE. The median dose in downstaged patients was 454 Gy, whereas the median doses in patients who had partial response/stable disease or progression were 248 and 138 Gy respectively ($P = 0.001$). Injected activities (GBq) were numerically higher in the downstaged patients than in the other groups, but the difference did not reach statistical significance.

Overall median survival was 26 months for the entire cohort. Median survival for the patients in the downstaged, partial response/stable disease and progressive disease was

Table 2 Survivals, administered energy and absorbed dose in the three group of patients: downstaged to surgery, partial response/stable disease and progression despite radioembolization

Group	Downstaged	Partial response/stable disease	Progressive disease	P value
Patient's number	5	8	11	
Mean survival [95% CI] (months)	54 [17–92]	30 [18–42]	11 [8–14]	0.001
Median survival \pm S.E. (months)	70 \pm 30	24 \pm 14	11 \pm 4	0.001
Administered activity (Gbg) (median \pm SD)	2.0 \pm 0.1	1.7 \pm 0.2	1.6 \pm 0.3	0.098
Tumor absorbed dose (Gy)	454 \pm 157	248 \pm 144	138 \pm 63	0.005

**Figure 1** Patient 3, trisectionectomy after one year from TARE (tumor necrosis: 90%). TARE, transarterial radioembolization.**Figure 2** Patient 4, trisectionectomy after six months from TARE (tumor necrosis: 85%). TARE, transarterial radioembolization.

70, 24 and 11 months respectively. A direct significant correlation was found between the tumor absorbed dose and patients' survivals ($P < 0.001$) (Table 2).

Treatment outcomes after downstaging to surgery

Patient 1 was a 72-year-old man with 3 confluent nodules and an overall tumor size of 12 cm in the right lobe with a first order branch tumor thrombus in HCV-related cirrhosis. He received a first TARE in June 2011 and a second procedure was performed 6 months later. He was reevaluated for surgery and underwent a right trisectionectomy in October 2012. In November 2014 he underwent conventional TACE for HCC recurrence in the left lobe. Hepatic decompensation occurred in March 2017 and the patient died in August 2017, 75 months after the first TARE.

Patient 2 was a 64-year-old man with metabolic cirrhosis and a single 8-cm HCC in the segment 8 with a second-order branch infiltration of the portal vein and of the suprahepatic vein branch. In December 2011 he underwent TARE and experienced a complete radiologic response

and a progressive reduction in the lesion size up to 3 cm. According to the study protocol, he was eligible to liver resection at both 6- and 12-month follow-up evaluation. However, he was referred for liver transplant, which was performed in 2013. As of this report, he is still alive 81 months after TARE.

Patient 3 was a 75-year-old man who had HCV-related cirrhosis and a single 8-cm HCC in the segment 4 infiltrating a second-order branch of the portal vein. He underwent TARE in November 2012 and a second procedure 6 months later. In November 2013 he underwent a right trisectionectomy (Figure 1). He is still alive, without recurrence and has a good performance status 70 months after the first TARE.

Patient 4 was a 74-year-old man who has HCV-related liver cirrhosis and two HCC nodules of 5 and 3 cm with a second-branch portal infiltration. In June 2013 TARE was performed. He received a right trisectionectomy 6 months after TARE (Figure 2). Two years later radiofrequency ablation (RFA) was performed for a 2-cm recurrence within segment 2 with complete response. He was classified as Child-Pugh B8 for liver function in march 2016, when he

died from a stroke without HCC recurrence, 33 months after the first TARE.

Patient 5 was a 73-year-old man who had HCV-related liver cirrhosis with a 7-cm HCC in segments 5–8 and two nodules (2 and 2.5 cm) in segments 4–5 with second-branch portal infiltration. He underwent TARE in December 2013. The major lesion was shrunken to 4 cm by 6 months after TARE but contrast enhancing tissue persisted. A second TARE was not performed because of the appearance of arteriovenous fistulas. In June 2014 he underwent a right trisectionectomy. CT was performed 3 months later and revealed bone and lymph node metastases. Patient died in December 2014, 12 months after the first TARE procedure.

Treatment-related toxicities

No radiation pneumonitis or radiation induced liver disease (RILD) or grade 3–4 adverse effects were observed after the treatment. The most common clinical side-effects were anorexia, fever and abdominal pain in 10/24 patients (41.7%), transient increase in liver enzymes and bilirubin in 9/24 patients (37.5%), worsening of the Child-Pugh score in 4/24 patients (17%) and persistent reduction of platelet count in 3/24 patients (12.5%).

Discussion

In our institutional experience, 5/24 patients (21%) or 5/28 (18% in an intention-to-treat analysis) who had unresectable, locally advanced HCC and cirrhosis were able to be downstaged to a surgical curative-intent treatment after radioembolization with 90-yttrium resin microspheres. Survivals for these patients were extended and comparable to the survival rates of well-selected patients who are eligible for surgery at the first presentation of HCC (5). This study is a further proof of concept of the potential role of TARE in this context. We do report downstaging rates that are comparable to another Spanish study that used resin microspheres (6 of 21 patients) (22). Differently, we have not found a correlation between a successful downstaging and patients' age or larger tumor volumes, as they did, but, in our series, high tumor absorbed radiation dose and low pre-treatment AFP level were the only variables significantly associated with the probability of achieve downstaging and consequently with longer survival. The 5 patients that had HCC downstaged received a median absorbed dose of 454 Gy, much higher than the minimal tumoricidal dose reported for resin microspheres (18)

and significantly higher than median absorbed dose of the other two groups. We calculated for every patient the maximum activity of yttrium-90 microspheres in order to deliver the highest dose to the tumor respecting the threshold of 40 Gy to the cirrhotic liver and 30 Gy to the lung. Therefore, the different absorbed doses depend on the two variables on which it is not possible to intervene, i.e., the arterial flow and the vessel density of the tumor. Even though variability in AFP levels existed within each group, mean pretreatment AFP values were lower in the patients with HCC that were successfully downstaged than in the patients who experienced partial response/stable disease or progressive disease. In our opinion, this is not surprising, because AFP has been identified as a predictor of biological aggressiveness of the tumor and the presence of vascular invasion (23,24).

At present, sorafenib, a multikinase inhibitor administered as continuous oral dosing, remains the standard of care for advanced HCC. Two large multicentric trials have recently compared radioembolization to sorafenib. Overall survivals were similar in both studies but adverse effects rates were significantly lower in the radioembolization group (25,26). TARE is therefore more tolerable than sorafenib but, moreover, it is able to rescue unresectable HCC to surgery.

Our study highlights that about twenty per cent of patients with locally advanced unresectable HCC who receive as first-line treatment radioembolization may be rescued to a surgical curative treatment with a good quality of life and a significant increase in their survival. Our results are encouraging but deserve to be confirmed in large studies. A high number of patients enrolled with a control arm, and a better definition of the criteria of resectability less related to the subjectivity of the surgeon are needed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy

or integrity of any part of the work are appropriately investigated and resolved. The corresponding Authors declare that the study was approved by the ethical committee of Mauriziano Hospital registration number IRB 11-368 and informed consent was taken from all patients.

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